Chapter 12: Congenital Rubella Syndrome

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I. Disease description

Rubella is a viral illness caused by a togavirus of the genus *Rubivirus* and is characterized by a mild, maculopapular rash. The rubella rash is sometimes misdiagnosed as measles or scarlet fever and occurs in up to 50% of rubella-infected persons. Children usually develop few or no constitutional symptoms, but adults may experience a 1–5 day prodrome of low-grade fever, headache, malaise, mild coryza, and conjunctivitis. Arthralgia or arthritis may occur in up to 70% of adult women with rubella. When rubella infection occurs during pregnancy, especially during the first trimester, the risk of fetal infection may be as high as 90%. Consequences of congenital rubella infection include abortions, miscarriages, stillbirths, and a constellation of severe birth defects known as congenital rubella syndrome (CRS). The most common congenital defects are cataracts, heart defects, sensorineural deafness, and developmental delay.

II. Background

The number of reported cases of congenital rubella syndrome in the United States has declined more than 92% from 77 cases in 1970 to a total of 6 cases in 1998.[1-3] Between 1990 and 1998, 100 cases of confirmed CRS were reported to the National Congenital Rubella Syndrome Registry. Of the cases with known import status, 76 were indigenous, and 22 were imported.

The goal of rubella vaccination is to prevent congenital rubella infection.

Despite routine rubella vaccination among children, rubella outbreaks continue in the U.S. These outbreaks are primarily confined to groups who traditionally refuse vaccinations and adults from countries without a history of routine rubella vaccination programs. Throughout the 1990s, the majority of infants with CRS are infants of mothers who fall into these categories.

III. Importance of rapid case identification

Infants with CRS should be identified as early in life as possible in order to prevent further spread of the virus. Additionally, early diagnosis will facilitate early intervention for specific disabilities. Infants with CRS may shed virus for a prolonged period and should be considered infectious until they are at least 1 year old or until two cultures of clinical specimens obtained 1 month apart are negative for rubella virus after age 3 months.

IV. Importance of surveillance

The goal of rubella vaccination is to prevent congenital rubella infection. Surveillance data are used to identify groups of persons or areas in which disease control efforts (such as immunization) can reduce disease incidence, and to evaluate the effectiveness of disease prevention programs and policies.

V. Disease reduction goals

As part of the proposed Healthy People 2010 objectives, a goal was established for the elimination of indigenous rubella and CRS in the United States by the year 2010.[4]

VI. Case definitions

The following case definition for congenital rubella syndrome was approved by the Council of State and Territorial Epidemiologists (CSTE) in June 1999.[5]

Clinical case definition

An illness, usually manifesting in infancy, resulting from rubella infection *in utero* and characterized by signs or symptoms from the following categories:

- Cataracts/congenital glaucoma, congenital heart disease (most commonly patent ductus arteriosus or peripheral pulmonary artery stenosis), loss of hearing, pigmentary retinopathy.

- Purpura, hepatosplenomegaly, jaundice, microcephaly, developmental delay, meningoencephalitis, radiolucent bone disease.

Clinical description

Presence of any defect(s) or laboratory data consistent with congenital rubella infection. Infants with CRS usually present with more than one sign or symptom consistent with congenital rubella infection. However, infants may present with a single defect. Deafness is the most common single defect.

Laboratory criteria for diagnosis

- Isolation of rubella virus, or

- Demonstration of rubella-specific immunoglobulin M (IgM) antibody, or

- Infant rubella antibody level that persists at a higher level and for a longer period than expected from passive transfer of maternal antibody (i.e., rubella titer that does not drop at the expected rate of a twofold dilution per month).

- Detection of rubella virus by polymerase chain reaction (PCR)

Case classification

Suspected: A case with some compatible clinical findings but not meeting the criteria for a probable case.

Probable: A case that is not laboratory confirmed and that has any two complications listed in first paragraph of the clinical case definition or one

complication from first paragraph and one from second paragraph, and lacks evidence of any other etiology.

Confirmed: A clinically consistent case that is laboratory confirmed.

Infection only: A case that demonstrates laboratory evidence of infection, but without any clinical symptoms or signs.

Note: In probable cases, either or both of the eye-related findings (cataracts and congenital glaucoma) count as a single complication. In cases classified as infection only, if any compatible signs or symptoms (e.g., hearing loss) are identified later, the case is reclassified as confirmed.

Indigenous case. Any case which cannot be proved to be imported.

Imported case. A case which has its source outside the reporting state.

- **International importation**. Defined as CRS in a U.S. or non-U.S. citizen whose mother was outside the United States for the entire period when she may have had exposure to rubella (21 days before conception and during the first 20 weeks of gestation), or who has known exposure to risks outside the United States.

- **Importation from another state**. This classification requires documentation that the mother either had face-to-face contact with a case of rubella outside the state, or was out of state for the entire period when he or she might have become infected (14–23 days before rash onset or 21 days before conception and during the first 20 weeks of gestation).

VII. Laboratory Testing

Diagnostic tests used to confirm CRS include serologic assays and isolation of the virus.

Laboratory confirmation can be obtained by any of the following:

- Demonstration of rubella-specific IgM antibodies in the infant's cord blood or sera. In infants with CRS, IgM antibody persists for at least 6-12 months. In some instances, IgM may not be detected until at least 1 month of age;

- Documentation of persistence of serum rubella IgG titer beyond the time expected from passive transfer of maternal IgG antibody;

- Isolation of rubella virus, which may be shed from the throat and urine for a year or longer; or

- Detection of rubella virus by polymerase chain reaction (PCR).

For additional information on use of laboratory testing in surveillance of vaccine-preventable diseases, see Chapter 19.

Serologic testing

The serologic tests available for laboratory confirmation of CRS infections vary among laboratories. The following tests are widely available and may be used for screening for laboratory confirmation of disease. The state health department can provide guidance on available laboratory services and preferred tests.

- **Enzyme immunoassays (EIA).** EIA is sensitive, widely available, and relatively easy to perform. It can also be modified to measure IgM antibodies. Most of the diagnostic testing done for rubella antibodies uses some variation of the EIA.

- **Immunofluorescent antibody assays (IFA).** IFA is a rapid and sensitive assay. Commercial assays for both IgG and IgM are available in the United States. Care must be taken with the IgM assay to avoid false-positive results due to complexes with rheumatoid antibody.

Virus isolation

Rubella virus can be isolated from nasal, blood, throat, urine, and cerebrospinal fluid specimens from rubella and CRS cases. Efforts should be made to obtain clinical specimens (particularly pharyngeal swabs and urine specimens) for virus isolation from infants at the time of the initial investigation (Appendix 17). However, infants with CRS may shed virus for a prolonged period so specimens obtained later may also yield rubella virus. Specimens for virus isolation (urine specimens and pharyngeal swabs) should be obtained monthly until cultures are twice repeatedly negative.

Virus isolates are extremely important for molecular epidemiologic surveillance to help determine the origin of the virus, the virus strains circulating in the U.S., and whether these strains have become endemic in the U.S.

Molecular typing

Virus isolates are extremely important for molecular epidemiologic surveillance to help determine 1) the origin of the virus, 2) virus strains circulating in the U.S., and 3) whether these strains have become endemic in the U.S.[6] Specimens for molecular typing should be obtained from patients with CRS as soon as possible after diagnosis. Appropriate specimens include pharyngeal swabs, cerebral spinal fluid, and cataracts from surgery. Specimens for virus isolation should be sent to CDC for molecular typing as directed by the state health department.

Polymerase chain reaction (PCR)

In the United Kingdom, there has been extensive evaluation of PCR for detection of rubella virus in clinical specimens, documenting its usefulness.[7,8] Clinical specimens obtained for virus isolation and sent to CDC are routinely screened by PCR. Further validation is needed of classification of cases that test positive by PCR in the absence of virus isolation.

VIII. Reporting

Each state and territory has regulations and/or laws governing the reporting of diseases and conditions of public health importance (Appendix 2).[9] These regulations/laws list the diseases which are to be reported, and describe those persons or groups responsible for reporting, such as health-care providers, hospitals, laboratories, schools, day care facilities, and other institutions. Contact your state health department for reporting requirements in your state.

Reporting to CDC

Provisional reports of rubella and CRS cases should be sent by the state health department to CDC via the National Electronic Telecommunications System for Surveillance (NETSS) within 14 days of the initial report to the state or local health department. Reporting should not be delayed because of incomplete information or lack of confirmation.

In addition, each possible and confirmed case of CRS should be reported to the National Congenital Rubella Syndrome Registry (NCRSR), National Immunization Program (NIP), CDC. The NCRSR case report form (Appendix 19) is used to collect clinical and laboratory information on cases of CRS that are reported by state and local health departments. NCRSR cases are classified by year of patient's birth. Although case report forms should be as complete as possible before case reporting, lack of complete information should not delay the reporting.

Information to collect

The following data are epidemiologically important and should be collected in the course of case investigation. Additional information may also be collected at the direction of the state health department.

- Demographic information

- Maternal history including
  —Date of rubella vaccination(s)
  —Dates and results of previous serologic tests for rubella immunity
  —History or documentation of rubella infection during pregnancy
  —History of pregnancies within and outside of the U.S.
  —Country of birth and time of residence in the U.S.

- Clinical details (e.g., cataracts, hearing loss, developmental delay, type of congenital heart defect, meningoencephalitis, microcephaly)

- Laboratory information including types and results of laboratory testing performed on both mother and child

IX. Vaccination

Although use of rubella vaccine is contraindicated in pregnant women or women planning pregnancy within 3 months, inadvertent administration of the vaccine to pregnant women does occur. In order to evaluate the risk to the fetus of exposure to attenuated rubella vaccine virus, a pregnancy registry was established. By April 1989 when the registry was discontinued, vaccination of 700 women with the RA 27/3 rubella vaccine within 3 months of conception was reported. Among the 289 women who were known to be susceptible at the time of vaccination, outcomes of pregnancy were known for 275 (94%); 83% delivered living infants, all 229 of whom were free of defects associated with CRS. Rubella-specific IgM was detected in three infants, but all three were normal on physical examination. These data are consistent with results reported from other countries, suggesting that if live attenuated rubella vaccine causes defects associated with CRS, it does so at a very low rate (<1.6%).

X. Enhancing Surveillance

The following activities may be undertaken to improve the detection and reporting of cases, and to improve the comprehensiveness and quality of surveillance for rubella and CRS. Additional guidelines for enhancing surveillance are given in Chapter 16.

Promoting awareness that rubella and CRS still occur in the United States. Efforts should be made to promote physicians' awareness of the possibility of rubella and CRS, especially when evaluating patients with suspected measles who have negative serologic tests for acute measles infection, (i.e., negative serum measles IgM).

Promoting awareness of high risks groups for rubella infection and CRS births. Rubella vaccine is not administered routinely in many countries, and in others rubella vaccine was only recently added to the childhood immunization schedule.[10] Thus, many persons born outside the United States or who received childhood immunizations in other countries never had the opportunity to receive rubella vaccine. Health-care providers should have a heightened index of suspicion of rubella and CRS births in individuals from countries without a history of routine rubella vaccination programs.

Active surveillance. Following an outbreak of rubella, an active surveillance system for CRS should be established among health-care providers, clinics, and hospitals in the outbreak area beginning 6–9 months after the rubella outbreak. Women who contracted rubella while pregnant should be monitored for birth outcome and a rubella-specific IgM antibody test performed on the infant after birth. Health care providers should be advised to evaluate infants born with conditions consistent with CRS and to perform a rubella-specific IgM antibody test on infants suspected of having CRS.

Searching laboratory records. Audits of laboratory records may provide

reliable evidence of previously unreported serologically confirmed or culture-confirmed cases of congenital rubella syndrome. Infants with CRS have been identified by including the serological results for TORCH agents in audits of laboratory records.

Comparing other data sets. Birth defects registries may reveal unreported CRS cases.[1] In addition, schools of the deaf and/or blind may have children with CRS enrolled who were never reported. Pediatric specialty clinics caring for children with mental retardation, congenital heart defects, congenital deafness, congenital cataracts, and growth retardation may be a source of unreported CRS patients. These activities should be undertaken following rubella outbreaks as part of enhancing surveillance for CRS.

Review of hospital discharge data and linkages with newborn hearing screening programs. Reviewing hospital discharge data in high-risk areas has proven useful in identifying undiagnosed cases of CRS.[11] Infants with discharge codes consistent with CRS may then be categorized according to the CRS case definition, allowing for greater insight into the rates of CRS in high-risk populations. Furthermore, if newborn hearing screening is routinely performed, infants identified through screening with hearing deficiencies or progressive hearing loss may also be tested for CRS, as deafness is the most common single defect associated with CRS.

XI. Case investigation

The diagnosis of a single case of CRS in a community should trigger intensified rubella and CRS surveillance.

Cases of CRS are sentinel events indicating the presence of rubella infections in the community which may have been previously unrecognized. The diagnosis of a single case of CRS in a community should trigger intensified rubella and CRS surveillance.

Infants with CRS may present with different manifestations of the syndrome depending on timing of the infection in pregnancy. The classic presentation for CRS is cataracts, deafness, and congenital heart disease (especially patent ductus arteriosus or peripheral pulmonic stenosis). Infants born to women infected with rubella should be evaluated for infection and CRS; however, symptoms may not be apparent depending on the gestational age of the infant at the time of the mother's infection. After 20 weeks gestation, the only defect may be deafness. Also, some children are only infected and have no congenital defects.

Laboratory confirmation should be sought in all suspected CRS cases. Regardless of signs or symptoms, a cord blood or sera to be tested for rubella IgM and urine and pharyngeal specimens for viral isolation should be obtained. In the event of a negative IgM result from a specimen taken within 1 month of birth, a second specimen should be obtained and tested once the infant is at least 1 month of age. A CRS case report form (Appendix 19) should be completed.

Efforts should be made to obtain clinical specimens (pharyngeal swabs and urine) for virus isolation from all cases. These isolates are essential for

tracking the epidemiology of rubella in the United States, now that rubella virus is believed to no longer continuously circulate in this country. By comparing isolates from new case-patients with other rubella virus samples, the origin of particular virus types in this country can be tracked.[6] See Appendix 17 for the procedure for collection of specimens.

XII. Prevention of transmission from infants with CRS

Cases of rubella have occurred among susceptible persons providing care for infants with CRS.[12] Infants with CRS can shed the virus for prolonged periods of time. Persons having contact with infants with CRS should be immune to rubella. Infants with CRS should be placed in contact isolation. These precautions should be enforced during any admission before the first birthday, unless two cultures of pharyngeal and urine specimens obtained one month apart are negative for virus after age 3 months.[13] ❖

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